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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/902,481	07/09/2001	Stephen Mayo	A-70586-1/RFT/RMS/RMK	5918

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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	20

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/902,481	MAYO ET AL.	
	Examin r	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,14 and 29-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *31-33* is/are allowed.

6)☒ Claim(s) *1-7,14 and 29-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8&13* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. Claims 1-7, 14 and 29-33 are pending and under examination.

2. Applicant's election without traverse of Group I, claims 1-7, 14 and 29-30 (now claims 1-7, 14 and 29-33) drawn to a structurally biased integrin I domain, wherein the alterations to the protein occur in at least two noncontiguous regions and a pharmaceutical composition filed on 4/29/03, is acknowledged.

3. The specification is objected to under 37 CFR 1.821(d) for failing to provide a sequence identifier for each individual sequence. Page 29 lines 1-7 has describe 10 amino acid sequences that each must have a sequence identifier. Correction is required.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-7, 14 and 29-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-7 and 14 are indefinite in the recitation of "integrin I domain", it is unclear which I domain is being referred to, it is unclear if the integrin I domain is αM, αL, α2 or α1 I domain.

B. Claims 1 and 29-30 are indefinite and ambiguous in the recitation of "about 98% identical to human integrin I domain" in the claim 1, 2nd line, and "98% identical to the wild-type protein" in claims 29 and 30, 3rd line. Recitation of percentage homology without providing SEQ ID NO for the protein is indefinite and ambiguous because different laboratories may have the same name of a different protein. Further, it is not clear whether the reference protein is derived from human, mouse, rat or other species.

C. Claims 3-7 indefinite and ambiguous in the recitation of "substitutions are selected from the amino acid residues at positions selected from positions 139, 153, 156, 157, 160, 199, 215, 219, 223, 238, 239, 240, 259, 269, 271, 299, 308" in claim 3 lines 3-4, " substitutions at positions 156, 160, 199, 215, 238, 239, 240, 259, 269, 271, 287, 299, 308" in claim 4 line 2, " substitutions at position 139, 153, 157, 199, 238, 239, 287, 299" in claim 5 line 2, "substitutions at positions 139, 153, 157, 199, 238, 239, 287, 299" in claim 6, line 2 and " substitutions at positions 215, 219, 223, 238" in claim 7, line 2. Recitation of amino acid positions without providing SEQ ID NO for the protein is

indefinite and ambiguous because different laboratories may have different numbering system of the same protein.

D. Claim 3 is indefinite for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of ..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y). Alternatively, deletion of "selected from positions" and insertion of "or" before the last species "308".

E. Claims 4-7 are indefinite for being in improper format. It is unclear whether any one, combination or all the specific positions are substituted.

F. Claim 1 is indefinite for reciting "less than about" in line 2. It is unclear how what percentage constitutes "less than about". One of skill in the art would not know if applicant meant 1%, as many as 50%, or even more.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-7, 14 and 29-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a non-naturally occurring integrin I domain protein of SEQ ID NOS: 3 (ido1q), 4 (ido1r) and 5 (ido2r) for stabilizing the integrin I domain in the open conformation and SEQ ID NO: 6 (jlm2r) for close conformation, and a composition thereof does not reasonably provide **enablement** for any structurally biased "integrin I domain protein" comprising an amino acid sequence that is less than about 98% identical to human integrin I domain protein wherein the alterations to the protein occur in at least two noncontiguous regions wherein said integrin I domain protein is artificially biased to exist in a "open" conformation in claim 1, any full length integrin comprising the said domain in claim 2, any non-naturally occurring integrin I domain protein comprising at least 3 amino acid substitutions as compared to human integrin I domain protein, wherein at least 2 of said substitutions are selected from the amino acid residues at positions 139, 153, 156, 157, 160, 199, 215, 219, 223, 238, 239, 240, 259, 269, 271, 299 or 308 in claim 3; a pharmaceutical composition comprising an integrin I domain protein according claim 1, 2, or 3 and a pharmaceutical carrier in claim 14 or a composition comprising "any integrin" that is artificially biased to exist in the open/closed conformation, where the artificial bias is a result of noncontiguous alteration of the protein, these alterations results in a protein that is less than 98% identical to the "wild-type protein", crystallized with "a ligand" in claims 29/30. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546(BPAI 1986). They include the nature of the invention, the state of the art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a structurally biased integrin I domain which effect the conformational structure of the integrin I domain.

The specification does not provide a sufficient enabling description of the claimed invention. The specification discloses only the amino acid sequence (SEQ ID NOs:3-5) with a disclosed open conformation (e.g., page 72 at line 18) and SEQ ID NO:6 with a disclosed close conformation. The instant claims encompass in their breadth *any* structurally biased integrin I domain protein comprising an amino acid sequence that is 1%-98% identical to human integrin I domain protein; or *any* non-naturally occurring integrin I domain protein comprising "at least 3 amino acid" substitutions, wherein "at least 2 of said substitutions" are selected form specific positions on the I domain, or any composition comprising "any integrin" that is artificially biased to exist in the open/close conformation, wherein the alterations resulting in a protein that is "less than 98%" identical to any wild-type protein, crystallized with any ligand.

One cannot extrapolate the teachings of the specification to the scope of the claims because the product claims are drawn to any structurally biased integrin I domain protein or to any integrin that is artificially biased. Applicant has not enabled any of these types of polypeptides because it has not been shown that these polypeptides are capable of existing as that which is being disclosed.

The specification discloses (page 72, line 18) that the open ido1q ido1r and ido2r mutants (SEQ ID NOs:3-5 both stabilized the alphaM I domain in the 1ido conformation and destabilized it in the 1jlm conformation.

There is insufficient direction or objective evidence as to how to make and to how to use any structurally biased protein for the number of possibilities associated with the myriad of direct and indirect effects associated with various polypeptides and, in turn, as to whether such a desired effect can be achieved or predicted, as encompassed by the claims. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the structure of any " integrin I domain" and still provide or maintain the claimed "open" conformation is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Because of this lack of guidance, an undue experimentation would be required to determine which modifications would be acceptable to retain occluding structural and functional activity, and the fact that the relationship between the sequence of a protein/peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Ngo *et al* in the Protein Folding problem and Tertiary Structure prediction, 1994, Merz *et al.*, (ed), Birkhauser, Boston, MA, pp.433 and 492-495), it would require an undue amount of experimentation for one of skill in the art to arrive at the claimed polypeptides encompassed by the claimed invention.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Burgess et al (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similarly, Lazar et al. (Mol Cell Biol. 8:1247-1252, 1988) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagines did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what substitutions and mutations of the disclosed integrin I domain can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p 1306, col. 2). Thus, it would require undue experimentation of one skilled in the art to practice the claimed invention.

Also, at issue is whether or not the claimed composition would function as pharmaceutical composition. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the pharmaceutical composition as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed pharmaceutical composition are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success.

In view of the lack of sufficient guidance in the specification and a limited number of working examples, the unpredictability in the art and the breadth of the claims it would take an undue amount of experimentation for one skilled in the art to practice the invention as claimed.

8. Claims 1-7, 14 and 29-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a non-naturally occurring integrin I domain protein of SEQ ID NOS: 3 (ido1q), 4 (ido1r) and 5 (ido2r) for stabilizing the integrin I domain in the open conformation and SEQ ID NO: 6 (jlm2r) for close conformation, and a composition thereof.

Applicant is not in possession of any structurally biased "integrin I domain protein" comprising an amino acid sequence that is less than about 98% identical to human integrin I domain protein wherein the alterations to the protein occur in at least two noncontiguous regions wherein said integrin I domain protein is artificially biased to exist in a "open" conformation in claim 1, any full length integrin comprising the said domain in claim 2, any non-naturally occurring integrin I domain protein comprising at least 3 amino acid substitutions as compared to human integrin I domain protein, wherein at least 2 of said substitutions are selected from the amino acid residues at positions 139, 153, 156, 157, 160, 199, 215, 219, 223, 238, 239, 240, 259, 269, 271, 299 or 308 in claim 3; a pharmaceutical composition comprising an integrin I domain protein according claim 1, 2, or 3 and a pharmaceutical carrier in claim 14 or a composition comprising "any integrin" that is artificially biased to exist in the open/closed conformation, where the artificial bias is a result of noncontiguous alteration of the protein, these alterations results in a protein that is less than 98% identical to the "wild-type protein", crystallized with "a ligand" in claims 29/30.

Applicant has disclosed only amino acid of SEQ ID NOs: 3-6; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath

at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Huang et al (JBC, 270:19008-19016, 1995, IDS Ref # C22).

Huang et al teaches that mutant E218H/R221K/L224S (noncontiguous alterations) bound to ICAM-1 (open conformation) with nearly wild-type activity. Huang et al further teaches that I235V/T245S/S245K (noncontiguous alterations) mutant binding to ICAM-1 is depressed (close conformation) (see page 19012, I col., 3rd paragraph in particular). The referenced mutants are 98.5% identical (100-(3X198X100) to human integrin I domain because "about" would open the claims to read on the vicinity of 98%.

The reference teachings anticipate the claimed invention.

11. Claims 31-33 are allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
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July 14, 2003

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